

### **REMARKS**

Applicant respectfully requests entry of the amendments and reconsideration of the claims. Claim 1 has been amended to further clarify the claimed subject matter. Support for the amendment can be found at page 10, lines 1 to 5 and elsewhere in the specification. Please cancel claim 20 without prejudice or disclaimer. Applicant reserves the right to file a continuation application on the cancelled subject matter. Claims 1-3 and 19 will be pending upon entry of the amendment. Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(b) and § 112, first paragraph.

Applicant also wishes to remind the Examiner of co-pending application serial number 10/761,596, which is a continuation of the instant application.

### **Restriction/Election**

The Examiner referred to an election with traverse of Group 1 (claims 1-2 and 8-17) and the ABX-EGF species in the reply of May 23, 2006 (page 3 of Office Action of May 16, 2007).

It would appear that the Examiner is inadvertently referring to a restriction/election from another application. Applicant requests clarification and withdrawal of the Examiner's restriction/election.

### **Rejection under 35 U.S.C. § 112, First Paragraph**

The Examiner rejects claims 1-3 and 19-20 under 35 U.S.C. § 112, first paragraph, on the basis that the specification, while being enabling for certain therapeutic nitric oxide donor compounds, including 3-morpholinisynthonimine (SIN-1), sodium nitrite, nitroprusside, and S-nitroso-N-acetyl-D, L-penicillamine (SNAP), the specification allegedly does not reasonably provide enablement for any therapeutic nitric oxide donor compound.

Applicant has cancelled claim 20. While the Applicant maintains that the subject matter of the claims as previously presented is fully enabled by the description, claim 1 has been

amended to define the therapeutic nitric oxide donor as being 3-morpholinisynndnonimine (SIN-1), sodium nitrite, nitroprusside, or S-nitroso-N-acetyl-D, L-penicillamine (SNAP) solely for the purpose of advancing the application to allowance. As the Examiner has acknowledged that the specification is enabling for these specific compounds, it is respectfully submitted that claims 1-3 and 19 are enabled as required by 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the Examiner's objection is respectfully requested.

**Rejection under 35 U.S.C. § 103(a)**

The Examiner rejects claims 1-3 and 19-20 as allegedly obvious over Adams et al. (US Patent 6,165,975; already made of record) in view of Lauth et al. (US Patent 5,561,165). Applicant respectfully traverses.

To make a *prima facie* case of obviousness, the teachings of the prior art should have suggested the claimed subject matter to the person of ordinary skill in the art, and all the claim limitations must be taught or suggested in the references cited by the Examiner. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). As articulated by the Supreme Court in a recent case, a combination is obvious if it is no more than the predictable use of known elements according to their established functions; and there was a reason to combine the known elements. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. \_\_\_\_ (2007). To make a *prima facie* case of obviousness, "it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." *Id.* The initial burden to make a *prima facie* case of obviousness is on the Examiner. *In re Bell*, 991 F.2d 781, 783 (Fed. Cir. 1993). Applicants submit that the Examiner does not make a *prima facie* case of obviousness because the Examiner has not established a reason to combine the known elements.

The Examiner cites the Adams et al. patent as teaching of method of treating a vascular condition (Office Action of May 16, 2007 at page 11, lines 3-4). Adams et al. disclose the "treatment of conditions concerned with peripheral vasoconstriction" (*See* Field of the Invention

at col. 1, lines 12-13). Specifically, Adams et al. describe and claim methods of treating vascular tone to treat erectile and sexual dysfunctions (See col. 1, lines 16-21; claims; etc.). It is in this context that Adams et al. cite the passage the Examiner relies upon, that a "number of investigators have *postulated* that ET antagonists could be used for...diabetes..." (col. 2, lines 24-31; *emphasis added*). "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. MPEP § 2141.02(VI); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). There is no teaching or suggestion that the administration of NO donors would affect endothelin in any other context besides vasoconstriction/vasodilation. More specifically, there is no teaching or suggestion that NO donors alone, or by mediating endothelin expression, would increase insulin sensitivity. The Examiner has not provided a connection between NO donors and insulin sensitivity.

Additionally, as recited above, a number of investigators have only *postulated* that ET antagonists could be used for diabetes. As the Supreme Court articulated in *KSR*, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." Since ET antagonists have only been *postulated* to affect diabetes, the Examiner has not provided *predictable* results to support a finding of obviousness. Applicants respectfully assert that the Examiner has not provided a connection between NO donors and insulin sensitivity, and there is not even a predictable extrapolation to diabetes in general.

Lautt et al. disclose the use of cholinergic agonists for increasing insulin responsiveness and improving glucose tolerance. Lautt et al. disclose that hepatic denervation causes insulin resistance. However, there is no suggestion that insulin resistance resulting from hepatic denervation or other form of hepatic autonomic dysfunction may be corrected by the administration of NO donors. There is no teaching or suggestion in Lautt et al. that parasympathetic neuropathy and insulin resistance is in any manner related to the actions of NO.

The Examiner has not provided a connection, or a motivation to explore, between NO donors and insulin responsiveness in view of Lauth et al.

The Examiner asserts in conclusion at page 12, lines 14-18 that

someone of skill... would have been motivated to combine the teaching of Adams et al. and Lauth et al. to create a method for increasing insulin sensitivity in a diabetic patient comprising administering the NO donor compounds taught by Adams et al.

However, an obviousness rejection where the relied upon references teach that all the aspects of the claims were individually known is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. MPEP § 2143.01(III); *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993); See also *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Applicants respectfully assert that the Examiner has not sufficiently established why a person of skill in the art would combine a reference describing the effects on NO and endothelin on vasoconstriction/vasodilation with a reference describing cholinergic agonists for increasing insulin responsiveness. Applicant respectfully asserts that the Examiner is using hindsight reconstruction to combine known elements that do not have a reason to be combined. *In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992). In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

### **Summary**

In view of the above amendments and remarks, the applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance

prosecution of this application, the Examiner is invited to telephone the undersigned at the below listed telephone number.

Respectfully submitted,

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